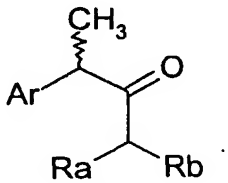
"CHIRAL ARYLKETONES IN THE TREATMENT OF NEUTROPHIL-DEPENDENT INFLAMMATORY DISEASES"

The present invention relates to chiral arylketones, a process for their preparation, and pharmaceutical compositions containing them, which are useful in the prevention and treatment of tissue damage due to the exacerbated recruitment of polymorphonucleate neutrophils in the inflammatory sites.

More specifically, the present invention relates to chiral arylketones of general formula I:



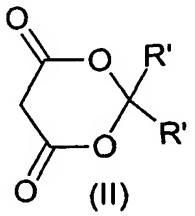
(I)

wherein:

Ar is an aryl group;

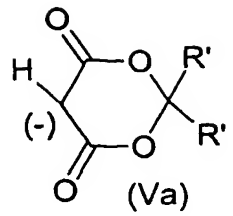
Ra and Rb are independently chosen in the group of hydrogen, linear or branched C_1-C_6 alkyl, phenyl, α-or β-naphthyl, 2, 3, 4-pyridyl, C_1-C_4-alkylphenyl, C_1-C_4-alkyl(α-or β-naphthyl), C_1-C_4-alkyl(2, 3, 4-pyridyl), cyano (-CN), carboxyamide, carboxyl or carboxyesters of formula CO_2R" wherein R" is the residue of a linear or branched C_1-C_6 aliphatic alcohol, a phosphonate $PO(OR")_2$ wherein R" is as defined above, a group of formula di-X-$(CH_2)_n$-Z, wherein X is a CO, SO, SO_2 group; Z is H, *tert*-butyl, isopropyl, CO_2R", CN, phenyl, α-or β-naphthyl, 2, 3, 4-pyridyl, C_3-C_6 cycloalkyl, NH-BOC, NH_2;

n is zero or an integer from 1 to 3; or Ra and Rb, with the carbon atom to which they are bound, form a cyclic residue 4, 6-dioxo-l, 3-dioxanyl-2, 2-disubstituted of formula II:



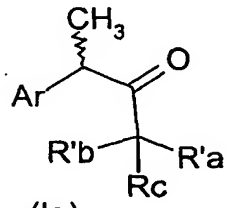
(II)

wherein R' is methyl or ethyl, or the two groups R' form a cyclohexane or cyclopentane ring.



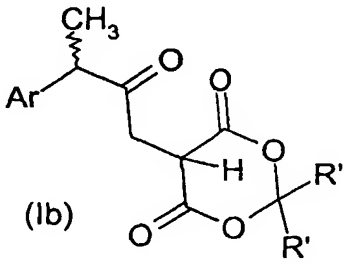
(Va)

wherein R' has the meanings indicated above, to yield a compound of formula (Ia):



(Ia)

wherein R'a, R'b and Rc have the meanings described above, provided that Rc is hydrogen when R'a and R'b with the carbon atom to which they are bound form 4, 6-dioxo-l, 3-dioxanyl of formula (II), also known as Meldrum adduct of formula Ib:



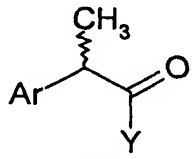
(Ib)

wherein Ar and R' have the meanings described above. If so desired, the Meldrum adducts are converted by boiling in a linear or branched C_1-C_6 alcohol into the corresponding β-ketoester of formula Ic:

(R, S) (±)-1, 3-dioxan-4, 6-dione-, 5-[2-(3-benzoylphenyl-1-oxopropyl)]-2, 2-dimethyl (CAS n° 154 023-15-1);

are known as racemic intermediates for the preparation of 2-arylpropionic acids [JP 03024023 (02.01.1991); JP 52108949 (09.12.1991); JP 52083426 (07.1.1977); JP 56097249 (08.05.1981); Tetr. Lett. 27. 4175, 1986] and of thiazoles [EP 511021; (28.10.1992); JP 0528902 (11.02.1993)].

The compounds of formula (I) are obtained by reacting an activated 2-arylpropionic acid of formula IV:

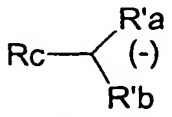


(IV)

wherein

Ar is as above defined aryl and Y is a residue activating the carbonyl, preferably a halogen, such as chlorine, 1-imidazolyl, pivaloyl, C_1-C_3-alkoxycarbonyl, succinyloxy, benzo-triazol-1-yloxy

with a carbanion of formula V:



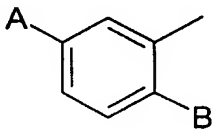
(V)

wherein:

- when R'a is the residue of a complex between a carboxyl and magnesium ethoxide, R'b is CO_2R'', $CONH_2$, CN, $PO(OR'')_2$ or -X-$(CH_2)_n$-Z', where X is as defined previously; Rc is H or -$(CH_2)_n$-Z', where Z' is H, *tert*-butyl, isopropyl, CO_2R'', CN, phenyl, α- or β-naphthyl, 2, 3, 4-pyridyl, C_3-C_6 cycloalkyl, NH-BOC;
- when R'a is hydrogen and Rc is hydrogen or a -$(CH_2)_n$-Z' radical, as defined above, R'b is phosphonate $PO(OR'')_2$, CO_2R'', or R'a and R'b with the carbon atom to which they are bound, form the carbanion at the carbon atom C_5 of a radical 2, 4-dioxo-l, 3-dioxanyl of formula Va:

By aryl group is meant preferably phenyl, optionally substituted by one to three substituents, which are the same or different from one another, selected from atoms of halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, hydroxy, C_1-C_4-acyloxy, phenoxy, cyano, nitro, amino, C_1-C_4-acylamino, halogen-C_1-C_3-alkyl, halogen C_1-C_3-alkoxy, benzoyl, or the aryl portion of known anti-inflammatory 2-aryl-propionic acids, such as ibuprofen, ketoprofen, naproxen, surprofen, carprofen, pirprofen, and fenoprofen.

Preferred residues of 2-aryl-propionic acid are: 4-iso-butyl-phenyl, 3-benzoylphenyl, 5-benzoyl-2-acetoxy-phenyl, 3-phenoxy-phenyl, 5-benzoyl-2-thiophenyl, 4-thienoyl-phenyl, 1-oxo-2-isoindolinyl-phenyl, 3-chloro-4-(2, 5-dihydro-1 H-pyrrol-l-yl)phenyl, 6-methoxy-β-naphthyl, l-hydroxy-phenyl-l-methyl, or a residue of formula III:



(III)

wherein A is benzyl, phenoxy, benzoyl, benzoyloxime, l-hydroxy-phenyl-l-methyl, B is hydroxy, C_1-C_4-acyloxy, or a group of formula -O-C(=S)-N$(CH_3)_2$; -S-C(=O)-N$(CH_3)_2$.

R is preferably an aryl residue of a known anti-infammatory 2-aryl-propionic acid, as defined above; more preferably, R represents: 4-(2-methyl-propyl)-phenyl, 3-phenoxy-phenyl, 3-benzoylphenyl, 2-[4-(1-oxo-2-isoindolinyl)phenyl], 5-benzoyl-thien-2-yl, 4-thienoyl-phenyl.

Preferred linear or branched C_1-C_6 alkyl and of a residue of C_1-C_6 aliphatic alcohol are methyl and ethyl; C_1-C_4 alkyl is preferably isobutyl; C_1-C_4-acyloxy is preferably acetyloxy.

Particularly preferred compounds of formula I of the invention are those compounds wherein the steric configuration of the carbon atom to which the residue R is bound corresponds to the configuration (R).

The following compounds:

(R, S) (±)-2-butanone, 3-[4-(2-methylpropyl)phenyl] (CAS n°-64758-90-3);

(R, S) (±)-2-butanone, 3-(3-phenoxyphenyl) (CAS n° 108671-27-8);

(R, S) (±)-2-butanone, 3-(3-benzoylphenyl) (CAS n° 79868-87-4);

ethyl (R, S) (±)-4-(3-benzoyl-phenyl)-3-oxo-pentanoate (CAS n° 145927-45-3);

malonic acids and their monosubstituted analogues or saponification of phosphonoacetic acids and 2-substituted analogues; sulfinylacetic and sulfonylacetic acids may be obtained by oxidation of ethers of thioglycolic acid. Alternatively, it is possible to use lithium enolates of formula V, obtained by reaction of lithium alkyls with known alkyl esters of alkylphosphonates (see, for example, N. Mongelli *et al.*, Synthesis, 310, 1988) or with esters of acetic acid (according to D.H. Harris *et al.*, Tetrah. Lett., 28, 2837, 1987).

For the preparation of enolates of formula Va, and more generally for the procedure of acylation of the cyclic alkylidenesters of malonic acid (also known as Meldrum acids) with the activated species of a carboxyl of formula IV, the method described by Y. Oikawa *et al.*, J. Org. Chem., 43, 2087 (1978), R.P. Houghton and D.J. Lapham, Synthesis 451 (1982) and C.C. Chan and X. Hung, *ibidem*, 452 (1982) is used.

The preparation of dialkoxyphosphonoacetic acids and that of their esters are exemplified in US 4151172 (April 24, 1979), or described by R.A. Malevannaya *et al.*, in Zh. Obshch. Khim. 41, 1426 (1971).

Specific examples of the compounds of the invention are:

methyl (R)(−)-4-[(4'-isobutyl)phenyl]-3-oxopentanoate;

methyl (S)(+)-4-[(4'-isobutyl)phenyl]-3-oxopentanoate;

(R,S) 4-[(4'-isobutyl)phenyl]-3-oxopentanoic acid;

methyl (R)(−)-4-[(3'-benzoyl)phenyl]-3-oxopentanoate;

(R)(−)-3-[(4'-isobutyl)phenyl]butan-2-one;

(S)(+)-3-[(4'-isobutyl)phenyl]butan-2-one;

(R)(−)-3-[(3'-benzoyl)phenyl]butan-2-one;

(R)(−)-dimethyl 3-(4-isobutyl)-2-oxobutan-1-phosphonate;

(S)(±)-dimethyl 3-(3'-phenoxy-phenyl)-2-oxo-butyl-1-phosphonate;

(R)(−)-2-(4-isobutylphenyl)-pentan-3-one;

(S) (+) ethyl-4-[(3'-benzoyl)phenyl]-3-oxopentanoate;

(S) (+)-3-[(3'-benzoyl)phenyl]butan-2-one;

(R)(−)-2-(4-isobutylphenyl)-4-phenyl-butan-3-one;

(R)(−)-2-(4-isobutylphenyl)-5-phenyl-pentan-3-one;

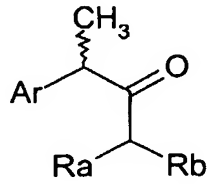
(R)(−)-2-(4-isobutylphenyl)-5-(pyrid-3-yl)-pentan-3-one;

(R)(-) methyl 4-[(4'-benzoyloxy)phenyl]-3-oxopentanoate;

(R)(-) methyl-4-[(4'-isopropylsulfonyloxy)phenyl]-3-oxopentanoate;

CLAIMS

1. (*R,S*)-1-Arylethylketone compounds of formula I and their single (*R*) and (*S*) enantiomers:



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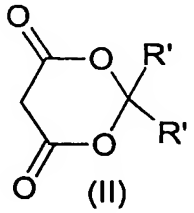
or Ra and Rb, with the carbon atom to which they are bound, form a cyclic residue 4, 6-dioxo-l, 3-dioxanyl-2, 2-disubstituted of formula II:



(II)

wherein R' is methyl or ethyl, or the two groups R' form a cyclohexane or cyclopentane ring with the exclusion of:

(*R, S*) (±)-2-butanone, 3-[4-(2-methylpropyl)phenyl];

(*R, S*) (±)-2-butanone, 3-(3-phenoxyphenyl);